

Kullo Lab Assertion Criteria 2016

***LDLR* Sequence Linked to Electronic Health Records**

Variants in *LDLR* (OMIM 606945) were classified using variant assertion concepts and principles adopted by the 2015 ACMG guidelines for the interpretation of sequence variants [PMID: 25741868].

Primary indication for testing: research

Incidental findings in *LDLR* were annotated based on scoring criteria encompassing (i) review of variant-level data, such as disease-specific variant frequency (0.3%), variant repositories, and *in-silico* pathogenicity scores, (ii) review of primary literature for the reported variants in the context of familial hypercholesterolemia (FH); dbSNP and dbVar were queried for *LDLR* variants and PubMed and Google Scholar searched using the following search terms: rsID and cDNA position for each variant, FH, secondary, and incidental findings, (iii) extensive EHR review including assessment of demographic data, low-density lipoprotein cholesterol (LDL-C) level and ascertaining Dutch Lipid Clinic Network (DLCN) criteria for FH comprising lipid levels, presence of personal or family history of premature atherosclerotic cardiovascular disease (ASCVD) and hypercholesterolemia, arcus cornealis and xanthomas.

Structured EHR data were mined for the highest untreated LDL-C levels. EHR-derived race and ethnicity data were used to calculate differences in variant frequency. Family history was defined as occurrence of ASCVD before age 55 in men and 65 years in women.

For post-hoc phenotyping we took a worst-case scenario approach when factoring DLCN criteria (≥ 3 points), i.e. when individuals had variability in the total score the highest value was taken into final computing; for the LDL-C levels we took a median to compare it with the threshold of 160 mg/dL (4.1 mmol/L).

DNA variation databases included NCBI-ClinVar and *LDLR*-LOVD.

For each variant the likelihood of altered LDL receptor activity was determined by an integrative score unifying different annotations from Polymorphism Phenotyping v2, SIFT, MutationTaster, MutationAssessor, Protein Variation Effect Analyzer.

Each component of the framework was assigned 0/1 point and a total score was computed for each selected variant: variants scored 4-5 were defined as likely pathogenic, 2-3 as variants of uncertain significance, and 0-1 as likely benign.

Web Resources:

NCBI ClinVar database, <http://www.ncbi.nlm.nih.gov/clinvar>

LDLR Leiden Open Variation, LOVD; versions 1.1.0 build 12, 2.0 build 36, and 3.0 build 13;
http://www.ucl.ac.uk/ldlr/LOVDv.1.1.0/index.php?select_db=LDLR

<http://www.ucl.ac.uk/ldlr>, https://grenada.lumc.nl/LOVD2/UCL-Heart/home.php?select_db=LDLR

http://databases.lovd.nl/whole_genome/genes/LDLR

NHLBI Exome Variant Server, EVS; <http://evs.gs.washington.edu/EVS/>

PolyPhen-2, <http://genetics.bwh.harvard.edu/pph2>

SIFT, <http://sift.jcvi.org>

MutationTaster, <http://www.mutationtaster.org/>

Mutationassessor, <https://omictools.com/mutationassessor-tool>

PROVEAN, <http://provean.jcvi.org/faq.php>

Article:

Safarova MS, Klee EW, Baudhuin LM, Winkler EM, Kluge ML, Bielinski SJ, Olson JE, Kullo IJ. Variability in assigning pathogenicity to incidental findings: insights from LDLR sequence linked to the electronic health record in 1013 individuals. *Eur J Hum Genet.* 2016; in press.